Supplement to:

A Phase 1b dose-escalation study of encorafenib (LGX818) and cetuximab with or without alpelisib in metastatic *BRAF*-mutant colorectal cancer

Supplementary Tables

Table S1. Pharmacokinetic parameters of encorafenib and alpelisib in patients at steady state (cycle 2 day 1).

Treatment	C_{max} (ng/mL)*	T_{max} (h)†	AUC_{tau} (h.ng/mL)*
Encorafenib PK in the dual-combination therapy group:			
100 mg encorafenib (*n* = 2; 2; 2)‡	1507±768	2 (1–2)	7662±2611
200 mg encorafenib (*n* = 6; 6; 6)	1427±824	2 (1–4)	7172±2888
400 mg encorafenib (*n* = 8; 8; 7)	3803±1314	2 (1–4)	15300±5640
450 mg encorafenib (*n* = 6; 6; 5)	5153±2564	2 (1–2)	16946±5757
Encorafenib PK in the triple-combination therapy group:			
200 mg encorafenib + 100 mg alpelisib (*n* = 3; 3; 3)	1552±534	2 (1–2)	6308±1190
200 mg encorafenib + 200 mg alpelisib (*n* = 7; 7; 6)	2427±2143	2 (1–6)	11079±3822
200 mg encorafenib + 300 mg alpelisib (*n* = 8; 8; 7)	2394±2077	3 (1–8)	12948±10649
300 mg encorafenib + 200 mg alpelisib (*n* = 3; 3; 1)	1595±876	2 (2–4)	5998
Alpelisib PK in the triple-combination therapy group:			
100 mg alpelisib + 200 mg encorafenib (*n* = 3; 3; 2)	680±93	2 (1–4)	5458±236
200 mg alpelisib + 200 mg encorafenib (*n* = 7; 7; 4)	2057±717	4 (1–6)	19673±2361
300 mg alpelisib + 200 mg encorafenib (*n* = 8; 8; 7)	2743±520	4 (2–6)	25126±3513
200 mg alpelisib + 300 mg encorafenib (*n* = 4; 4; 2)	1562±816	4 (4–8)	11179±3830

*Arithmetic mean ± standard deviation.
†Median (minimum – maximum) value.
‡Number of patients for C_{max}, T_{max}, AUC_{tau}, respectively. Some patients only had C_{max} and T_{max}, and AUC_{tau} could not be calculated (Phoenix PK software; version 6.2; Pharsight, St. Louis, MO) due to a lack of sufficient PK data.

Abbreviations: AUC_{tau}, area under the plasma concentration time curve for a dosing interval; C_{max}, maximum serum concentration; PK, pharmacokinetics; T_{max}, time of maximum serum concentration.

Table S2. Criteria for defining dose-limited toxicities

Toxicity	Any of the following criteria
Blood and lymphatic disorders*	• Febrile neutropenia (absolute neutrophil count <1.0 x 10^9/L with fever ≥38.5°C)†
Blood investigations	• Grade 3 absolute neutrophil count for >7 consecutive days or grade 4 absolute neutrophil count • Grade 3 platelet count for >7 consecutive days and/or with signs of bleeding or grade 4 platelet count
Skin and subcutaneous disorders	• Grade 3 rash/photosensitivity/hand-foot skin reaction (HFSR) for >7 consecutive days despite skin toxicity treatment or grade 4 rash/photosensitivity/HFSR
Metabolism and nutrition disorders‡	• Grade 2 hyperglycemia that does not resolve to grade 0 within 14 consecutive days (after initiation of oral antidiabetic treatment) • Grade 3 hyperglycemia for >7 consecutive days despite oral antidiabetic treatment • Grade 4 hyperglycemia or hyperglycemia that leads to diabetic ketoacidosis, hospitalization for IV insulin infusion, or non-ketotic coma
Gastrointestinal disorders	• ≥grade 3 vomiting or nausea or diarrhea lasting more than 48 h despite optimal therapy • ≥grade 3 pancreatitis
Renal investigations	• ≥grade 3 serum creatinine
Hepatic investigations§	• ≥grade 3 blood bilirubin • AST or ALT ≥3 x ULN in conjunction with blood bilirubin ≥2 x ULN of any duration • Grade 3 AST or ALT for >7 consecutive days or grade 4 AST or ALT • Grade 4 serum alkaline phosphatase for >7 consecutive days
Metabolic investigations	• Grade 3 lipase and/or serum amylase for >7 consecutive days or grade 4 lipase and/or serum amylase
Vascular disorders	• ≥grade 3 persistent hypertension requiring more than one drug or more intensive therapy than previously
Cardiac disorders	• ≥grade 3
Tumor lysis syndrome (TLS)	• ≥grade 4 TLS (life-threatening)**
General disorders	• Grade 3 fatigue for >7 consecutive days • ≥grade 3 edema for >14 consecutive days
Ophthalmologic disorders	• Grade 3 retinopathy/uveitis for >21 days or grade 4 retinopathy/uveitis confirmed by ophthalmologic examination • Any grade retinal vein occlusion • Any other eye disorders of grade 3 for >14 days or grade 4
Any other AE (excluding squamous cell carcinoma)††	• ≥grade 3

*≥grade 3 anemia was not considered a DLT unless judged to be a hemolytic process secondary to study drug. ≥grade 3 lymphopenia was not considered a DLT unless clinically significant.

†Not according to CTCAEv4.0.

‡Hyperglycemia occurring during corticosteroids administration was only considered a DLT if not resolved within 2 days after the end of corticosteroid treatment.

§For any grade ≥3 hepatic toxicity that did not resolve within 7 days to ≤grade 1 (or ≤grade 2 if liver infiltration with tumor present), an abdominal CT scan was performed to assess if it was related to disease progression.

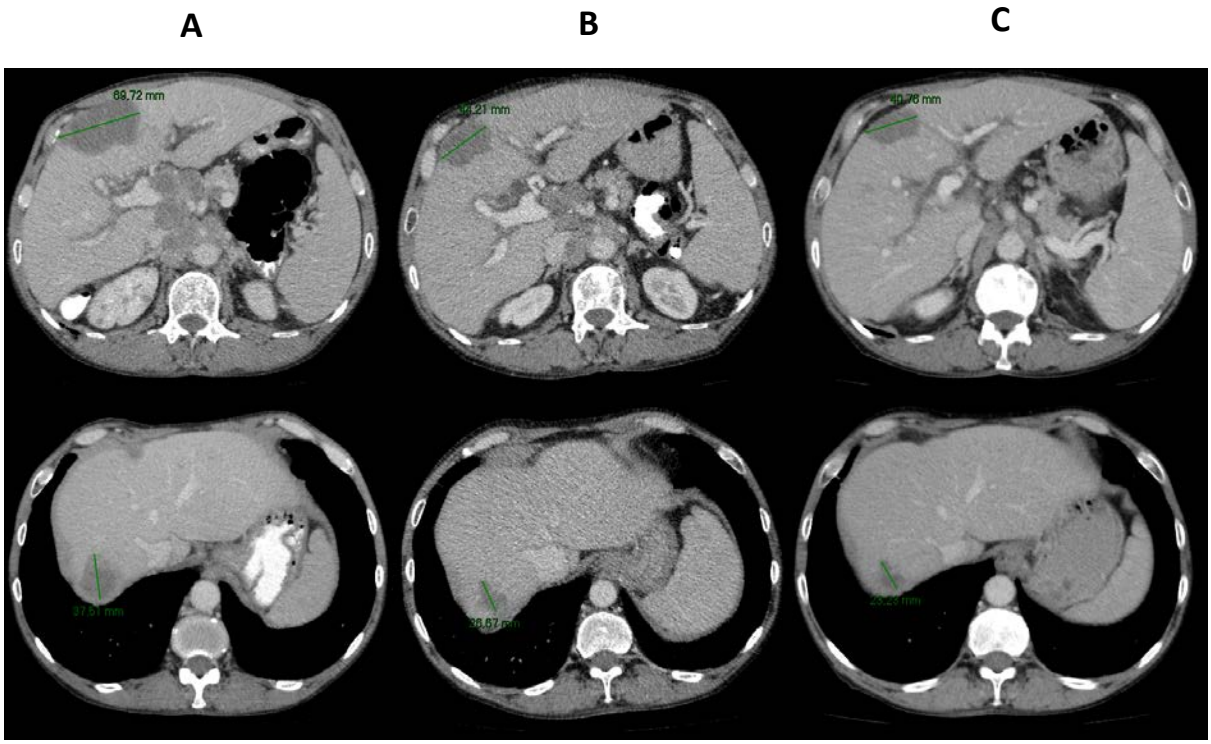
**All patients diagnosed with TLS were discussed with the sponsor as soon as possible after the diagnosis.

††An AE was required to be clinically significant to be defined as a DLT: study drug-related fever, alkaline phosphatase elevation, electrolyte abnormalities (including K, NA, Cl, HCO_3, Mg, Ca, PO_4) were not considered a DLT unless clinically significant. Squamous cell carcinoma has been reported as an on-target side effect of BRAF inhibitors that is manageable and will not be considered a DLT. Cetuximab-induced infusion reactions will not be considered a DLT.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; DLT, dose-limiting toxicity; ULN, upper limit of normal.

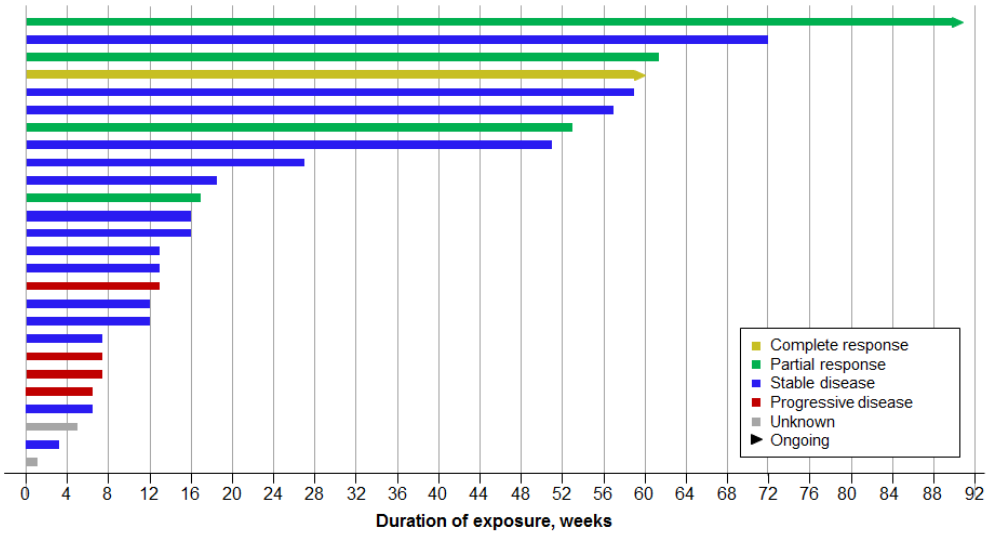
Supplementary Figures

Supplementary Figure 1. Radiological images of response for a patient treated with the dual-combination therapy of encorafenib and cetuximab A) at baseline, B) after 6 weeks of treatment: PR (–40%), and C) after 10 weeks of treatment: confirmed PR (–45%).



Supplementary Figure 2. Time on study by response for A) patients treated with the dual-combination therapy of encorafenib and cetuximab and B) patients treated with the triple-combination therapy of encorafenib, alpelisib, and cetuximab

A)



B)